

**I. REMARKS**

The Advisory Action indicates that the finality of the Official Action mailed February 17, 2010 has been maintained. Thus, the claim amendments submitted in the Response and Amendment filed June 15, 2010 were not entered by the Examiner because they allegedly "raise new issues that would require further consideration and/or search". Applicants respectfully note, however, that the Examiner has improperly maintained the finality of the Official Action February 17, 2010. Thus, the claim amendments submitted in the Response and Amendment filed June 15, 2010 should be entered as a matter of right. Accordingly, applicants respectfully request that the Examiner:

- 1) Withdraw the improper finality of the Official Action dated February 17, 2010;
- 2) Enter the claim amendments submitted June 15, 2010;
- 3) Fully consider the arguments in the Response and Amendment regarding the patentability of those claims submitted June 15, 2010; and
- 4) Fully consider the arguments outlined herein that support the patentability of these claims.

Upon entry of the claim amendments submitted June 15, 2010, claims 1-7, 9-11, 13, 14, 16 and 17-21 will be pending in the present application. Claims 8, 12 and 15 have been cancelled. Claims 9-11, 14 and 17-21 stand withdrawn.

## II. IMPROPER FINALITY OF OFFICIAL ACTION

In the Advisory Action mailed July 2, 2010, the Examiner has given absolutely no reasoning as to why the finality of the Official Action mailed February 17, 2010 was 1) either proper in the first place, or 2) was properly maintained in the Advisory Action. Instead, the Examiner made a cursory statement that "the finality is maintained".

Applicants again respectfully note that the Official Action mailed February 17, 2010 is improperly designated as "Final" since it contained a new rejection exists that was not necessitated by applicants' amendment filed November 12, 2009. In particular, on page 6 of the instant Official Action, the Examiner newly rejects claims 1-7, 13 and 16 under 35 U.S.C. §112, 2<sup>nd</sup> paragraph as being indefinite for reciting "which inhibits PDE10, comprising a structural element as an integral part of its overall structure, wherein said structure-element has the formula X ..."

Applicants respectfully note that this language was present in the claims as originally presented in the Preliminary Amendment filed December 23, 2005 with the instant application and was not previously rejected in the Official Action mailed June 12, 2009. It is respectfully submitted that this language was not amended with the last Response filed November 12, 2009. **Therefore, the Examiner's position that the rejection based on this language was necessitated by amendment is untenable.**

Applicants respectfully remind the Examiner that MPEP §706.07(a) states:

"Under present practice, second or any subsequent actions on the merits shall be final, except where the examiner introduces a new

ground of rejection that is neither necessitated by applicant's amendment of the claims, nor based on information submitted in an information disclosure statement..."

Because this new rejection under 35 U.S.C. §112 meets the first of these requirements (i.e. a new rejection not necessitated by applicants' amendment), **the finality of this Official Action is clearly improper.** Thus, the claim amendment submitted in the Response and Amendment filed June 15, 2010 should be entered by the Examiner as a **matter of right.**

Accordingly, applicants respectfully request that the Examiner withdraw the finality of the Official Action and enter the claim amendments submitted June 15, 2010.

### **III. REJECTION OF CLAIMS 1-7, 13 AND 16 UNDER 35 USC § 103(a)**

At page 2 of the Official Action mailed February 17, 2010, the Examiner states she has maintained her rejection of claims 1-7, 13 and 16 under 35 USC § 103(a) as being unpatentable over Bauser et al. (WO 03/014116), Zhang et al. (WO 03/51877) and Niewohner et al. (WO 02/048144) in view of GB 1153670, US 4694085 and Liebig's Ann. Chem. 9, 1534-1544 (1981).

### **RESPONSE**

The rejection is respectfully traversed. The Examiner has not established a *prima facie* case of obviousness against the presently pending claims.

To establish a *prima facie* case of obviousness, the PTO must satisfy three requirements. First, there must be some motivation or teaching in the

references cited by the Examiner to combine the separate elements taught in the separate references. As the U.S. Supreme Court held in *KSR International Co. v. Teleflex Inc. et al.*, 550 U.S. 398 (2007), "a court must ask whether the improvement is more than the predictable use of prior art elements according to their established functions. ...it [may] be necessary for a court to look to interrelated teachings of multiple patents; the effects of demands known to the design community or present in the marketplace; and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue. ...it can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does... because inventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known." See *KSR International Co. v. Teleflex Inc. et al.*, 550 U.S. 398 at 417-418. Second, the proposed modification of the prior art must have had a reasonable expectation of success, determined from the vantage point of the skilled artisan at the time the invention was made. *Amgen Inc. v. Chugai Pharm. Co.*, 18 USPQ2d 1016, 1023 (Fed. Cir. 1991). Lastly, the prior art references must teach or suggest all the limitations of the claims. *In re Wilson*, 165 USPQ 494, 496 (C.C.P.A. 1970).

The Examiner has stated on pages 2-3 of the Official Action that the cited references make the scope of the presently pending claims "obvious to try with a

finite number of identified, predictable solutions with a reasonable expectation of success.”

Applicants respectfully take issue with this statement. Each of the cited references disclose compounds that require a hydrogen substitution at both the R5- and R51-positions of the tricyclic scaffold. In contrast, the presently amended claims can only have “1-4C-alkyl, 1-4C-alkoxycarbonyl or cyano” at the R5-position of the tricyclic scaffold. Applicants have canceled the possibility of R5=H from the presently pending claims. Therefore, it is not understood how the Examiner concludes that the presently claimed subject matter represents “a finite number of identified, predictable solutions with a reasonable expectation of success.”

Furthermore, applicants’ comparative data which was presented in the Declaration filed November 12, 2009 clearly demonstrates unexpectedly superior results – not a “predictable solution” as alleged by the Examiner. In particular, the Declaration directly compares similar compounds which were tested wherein R5 = H was substituted for a compound that falls within the scope of currently pending claim 1 (i.e. wherein R5 = 1-4C-alkyl, 1-4C-alkoxycarbonyl or cyano.)

The Declaration clearly demonstrates that the compounds as claimed in presently pending claim 1 show a totally unexpected biological profile which by no means was suggested or implied by the compounds known from the art. In particular, the comparative data clearly shows that the presently claimed compounds have a superior pharmacological profile as PDE10 inhibiting

compounds, since they unexpectedly show an increased selectivity for PDE10 over PDE4 when compared to compounds from the art where R5 is hydrogen, and for six of the nine compounds, an increased potency regarding PDE10 inhibition.

These comparative findings are completely unexpected – not “predictable” as alleged by the Examiner - in view of the teachings of the prior art which merely show that compounds of formula 1 with R5 (and R51) being hydrogen are capable of inhibiting PDE10. As such, a person of ordinary skill in the art would not expect that replacing hydrogen in the R5 position by alkyl, alkoxy carbonyl, or cyano group would lead to compounds with an increased selectivity for PDE10 over PDE4, and in some respects, an increased potency regarding PDE10 inhibition.

As such, the presently rejected claims are unobvious over the cited references and withdrawal of this rejection is respectfully requested.

#### **IV. REJECTION OF CLAIMS 1-7, 13 AND 16 UNDER 35 USC § 103(a)**

At page 3 of the Official Action, the Examiner has maintained the rejection of claims 1-7, 13 and 16 under 35 USC § 103(a) as being unpatentable over Casagrande et al.

#### **RESPONSE**

The rejection is respectfully traversed. The Examiner has not established a prima facie case of obviousness against the presently pending claims.

Relevant authority regarding the requirements that the Examiner must

meet to establish a *prima facie* case of obviousness is outlined in Section III above.

Similar to each of the cited references that were discussed in Section III, the Casagrande et al. reference also does not disclose compounds with any substituent at the 5-position of the tricyclic scaffold other than hydrogen.

In contrast, the presently amended claims can only have "1-4C-alkyl, 1-4C-alkoxycarbonyl or cyano" at the 5-position of the tricyclic scaffold. Applicants have canceled the possibility of R5=H from the presently pending claims.

As such, applicants again refer to the unexpectedly superior results of the presently claimed compounds over those disclosed by the prior art as discussed in Section II and demonstrated in the attached Declaration. In particular, applicants respectfully submit that a person of ordinary skill in the art would not expect that replacing hydrogen in the R5 position by alkyl, alkoxycarbonyl, or cyano group would lead to compounds with an increased selectivity for PDE10 over PDE4, and in some respects, an increased potency regarding PDE10 inhibition.

Therefore, it is respectfully submitted that Casagrande et al. cannot render the presently pending claims obvious in view of the clear structural differences between the disclosed compounds and the presently claimed compounds. Further, any alleged finding of a *prima facie* case of obviousness is moot in view of the comparative data presented herein which clearly shows that the presently claimed subject matter is unexpectedly superior over the compounds of the prior art.

As such, the presently rejected claims are unobvious over the cited references and withdrawal of this rejection is respectfully requested.

**V. REJECTION OF CLAIMS 1-7 AND 11 UNDER 35 USC § 103(a)**

At page 3 of the Official Action, the Examiner has maintained the rejection of claims 1-7 and 11 under 35 USC § 103(a) as being unpatentable over Anderson et al.

**RESPONSE**

The rejection is respectfully traversed. The Examiner has not established a *prima facie* case of obviousness against the presently pending claims.

Relevant authority regarding the requirements that the Examiner must meet to establish a *prima facie* case of obviousness is outlined in Section III above.

Similar to each of the cited references that were discussed in Section III, the Anderson et al. reference also does not teach the presently amended compounds which contain substituents at the 5-position of the tricyclic scaffold other than hydrogen.

In fact, the presently amended claims can only have "1-4C-alkyl, 1-4C-alkoxycarbonyl or cyano" at the 5-position of the tricyclic scaffold. Applicants have canceled the possibility of R5=H from the presently pending claims.

As such, applicants again refer to the unexpectedly superior results of the presently claimed compounds over those disclosed by the prior art as discussed



in Section II and demonstrated in the attached Declaration. In particular, applicants respectfully submit that a person of ordinary skill in the art would not expect that replacing hydrogen in the R5 position by alkyl, alkoxycarbonyl, or cyano group would lead to compounds with an increased selectivity for PDE10 over PDE4, and in some respects, an increased potency regarding PDE10 inhibition.

Therefore, it is respectfully submitted that Anderson et al. cannot render the presently pending claims obvious in view of the clear structural differences between the disclosed compounds and the presently claimed compounds. Further, any alleged finding of a *prima facie* case of obviousness is moot in view of the comparative data presented herein which clearly shows that the presently claimed subject matter is unexpectedly superior over the compounds of the prior art.

As such, the presently rejected claims are unobvious over the cited references and withdrawal of this rejection is respectfully requested.

**VI. REJECTION OF CLAIM 1 UNDER 35 USC § 112, 1<sup>ST</sup> PARAGRAPH**

At page 4 of the Official Action, the Examiner has rejected claim 1 under 35 USC § 112, 1<sup>st</sup> paragraph as failing to comply with the written description requirement.

**RESPONSE**

The rejection is respectfully traversed.

In this regard, applicants note the Examiner's statement on page 6 that

"Even though some places R2 is a H, the scope [is] that R2 and R3 both are not hydrogen. Thus between R1, R2 and R3 the ring always has to have at least 2 substituents."

Applicants respectfully note that there is clear basis in the instant specification for R2 to be hydrogen. Applicants note the Examiner's acknowledgement in this regard. However, applicants note that claim 1 was amended in the Response and Amendment filed June 15, 2010 to recite that **both R2 and R3 cannot simultaneously be hydrogen.**

Basis for this amendment may be found throughout the specification as filed. In particular, basis may be found at page 2, definitions for R1, R2 and R3, page 3, definitions for R1, R2 and R3, page 6, definitions for R1, R2 and R3 (subaspect a1), page 7, definitions for R1, R2 and R3 (subaspect a2), pages 7-8, definitions for R1, R2 and R3 (subaspect a3), pages 8-9, definitions for R1, R2 and R3 (subaspect b1), page 9, definitions for R1, R2 and R3 (subaspect b2), page 10, definitions for R1, R2 and R3 (subaspect b3), page 10, definitions for R1, R2 and R3 (subaspect c1), page 11, definitions for R1, R2 and R3 (subaspect c2), page 11, definitions for R1, R2 and R3 (subaspect c3), page 11, definitions for R1, R2 and R3 (subaspect d1), page 12, definitions for R1, R2 and R3 (subaspect d2), page 12, definitions for R1, R2 and R3 (subaspect d3), page 12, definitions for R1, R2 and R3 (subaspect d4), page 13, definitions for R1, R2 and R3 (subaspect d5), page 13, definitions for R1, R2 and R3 (subaspect d6), and pages 14-15, definitions for R1, R2 and R3 (subaspect e1), including Table 1. In each of these sections of the instant specification, it is clear that R2 can be

defined as hydrogen, however, R2 and R3 are not hydrogen at the same time. Therefore, sufficient basis in the specification exists for this amendment.

Accordingly, reconsideration and withdrawal of this rejection is respectfully requested.

**VII. REJECTION OF CLAIMS 1-7, 13 AND 16 UNDER 35 USC § 112, 2<sup>ND</sup> PARAGRAPH**

At page 6 of the Official Action, the Examiner newly rejected claims 1-7, 13 and 16 under 35 USC § 112, 2<sup>nd</sup> paragraph as being indefinite.

**RESPONSE**

The rejection is respectfully traversed.

The Examiner states that the claimed language “which inhibits PDE10, comprising a structural element as an integral part of its overall structure, wherein said structure-element has the formula X ...” is vague and indefinite.

Applicants respectfully disagree. This language is perfectly clear in view of the disclosure contained in the specification. In particular, applicants respectfully direct the Examiner’s attention to the paragraph bridging pages 15-16 of the instant specification, wherein it is stated:

A further aspect of the present invention is a process to provide compounds, which inhibit PDE10, comprising the following steps:

a.) designing intellectually the structure of a compound comprising - as part of its overall structure - a structure-element of the formula X, Xa or Xb, in which R1, R2, R3, R4, R41, R5, R51, R6 and R8 have the meanings given above in the special aspect A, in particular, in the subaspects thereto, in more particular in the subaspects emphasized above;

b.) synthesizing materially a compound having said designed structure in a manner known to the person skilled in the art, or as disclosed in the specification of the present invention, or as disclosed in WO 02/48144, WO 03/014115, WO 03/014116 or WO 03/014117, or analogously or similarly thereto. (emphasis added)

Further, page 16, fourth full paragraph of the instant specification recites:

A further aspect of the present invention is a method to inhibit PDE10 comprising using a compound containing - as an integral part of its overall structure- a structure-element of the formula X, Xa or Xb, in which R1, R2, R3, R4, R41, R5, R51, R6 and R8 have the meanings given above in the special aspect A, particularly, in the subaspects thereto. (emphasis added)

Therefore, it would be clear to a person of ordinary skill in the art that formulae X, Xa and Xb are – themselves – part of the overall structure of a larger compound that is designed to inhibit PDE10.

Further, applicants respectfully point out that formulae X, Xa and Xb have each been amended to show that the 2-position of each of these formulae is an attachment point where these formulae attach to another residue.

Accordingly, reconsideration and withdrawal of this rejection is respectfully requested.

**VIII. CONCLUSION**

Applicants assert that the claims are in condition for immediate allowance and early notice to that effect is earnestly solicited. Should the Examiner deem that any further action by Applicants' undersigned representative is desirable and/or necessary, the Examiner is invited to telephone the undersigned at the number set forth below.

In the event this paper is not timely filed, Applicants petition for an appropriate extension of time. Please charge any fee deficiency or credit any overpayment to Deposit Account No. 14-0112.

Respectfully submitted,

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